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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	17

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/001,039	Jolly et al.
Examiner	**Group Art Unit**
Robert Schwartzman	1636

☒ Responsive to communication(s) filed on *Apr 17, 2000* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-11, 37-58, and 61-68* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

X Claim(s) *37-56* is/are allowed.

X Claim(s) *1-3, 6-11, 57, 58, and 61-68* is/are rejected.

X Claim(s) *4 and 5* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *5,12,14*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This Office action is in response to the amendment filed April 17, 2000 (Paper No. 15). Claims 1-11, 37-58 and 61-68 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-11, 58 and 61-68 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejections is maintained for the reasons of record in the previous Office action dated October 12, 1999.

To summarize the rejection, the claims are broad, the prior art indicates the difficulty in obtaining long term expression of a protein at significant levels, there is little correlation between results obtained in small mammals and humans, the specification provides little guidance in terms

of achieving long term expression and the working examples do not provide significant evidence of long term expression. Based on these factors it would clearly require undue experimentation for one of skill in the art to practice the claimed invention.

Applicants argue that the animal models show that statistically significant long-term expression can be achieved and request that evidence that the animal models provided are not indicative of utility in humans be provided.

These arguments have been fully considered but are not deemed to be persuasive. The previous Office action dated October 12, 1999 explicitly refers to reviews by two of the leaders in the field of gene therapy (Verma *et al.*, Anderson *et al.*) which specifically state that there is little correlation between results obtained in small mammals and the predictability of results in humans. Thus, evidence for a lack of correlation has been provided and it is now applicants' burden to overcome the *prima facie* case for lack of enablement. The specification provides no guidance as to why half of the experiments produced no positive results or why potential results in humans would correlate with the experiments that worked rather than the experiments that didn't work. In none of the examples is the protein expressed for the thirty days immediately following administration of the vector (*i.e.*, there is always a lag period following administration) so the examples are not an embodiment of the claim as currently written ("produced...for a period of at least 30 days after the administration"). Thus, the lack of correlation between the working

examples and the invention as claimed, as well as the lack of correlation between animal model results and results in humans, makes it clear that the specification does not enable one of skill in the art to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mulligan *et al.* in view of either Mason *et al.* or Takeuchi *et al.* This rejection is maintained for the reasons of record in the previous Office action dated October 12, 1999.

To summarize the rejection, Mulligan *et al.* teaches a replication defective retrovirus (MFG) encoding FVIII and capable of infecting human cells. The FVIII has an SQN deletion. Mulligan *et al.* does not teach retroviruses that are resistant to degradation by human complement. Mason *et al.* and Takeuchi *et al.* each teach retroviruses that are resistant to degradation by human complement. It would have been *prima facie* obvious to one of ordinary

skill in the art at the time the invention was made to make a retroviral vector encoding FVIII as taught by Mulligan *et al.* and to modify the retroviral vector to be resistant to degradation by human complement by the method of Mason *et al.* or Takeuchi *et al.*, motivated by the teaching of Mulligan *et al.* that the retroviral FVIII vector was intended for administration for humans and the teachings of Mason *et al.* and Takeuchi *et al.* that the complement-resistant retrovirus would be more efficient for *in vivo* gene delivery applications.

Applicants argue that the references do not provide a reasonable expectation of success in constructing complement-resistant retroviral particles capable of expression of FVIII which can be utilized in an *in vivo* clinical setting.

This argument has been fully considered but is not deemed to be persuasive. Applicants do not provide any reasoning or evidence to support the position that there is not a reasonable expectation of success. Furthermore, the claims are not drawn to retroviral particles which can be utilized in an *in vivo* clinical setting, just to retroviral particles, so an expectation of success *in vivo* is not required. The expectation that the vector could successfully be synthesized is extremely high. That is all that is necessary.

Claim 57 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Kay *et al.* in view of either Mason *et al.* or Takeuchi *et al.* This rejection is maintained for the reasons of record in the previous Office action dated October 12, 1999.

To summarize the rejection, Kay *et al.* teaches a replication defective retrovirus (LNCX) encoding factor IX (FIX) which is capable of infecting human cells. Kay *et al.* does not teach retroviruses that are resistant to degradation by human complement. Mason *et al.* and Takeuchi *et al.* each teach retroviruses that are resistant to degradation by human complement. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a retroviral vector encoding FIX as taught by Kay *et al.* and to modify the retroviral vector to be resistant to degradation by human complement by the method of Mason *et al.* or Takeuchi *et al.*, motivated by the teaching of Kay *et al.* that the retroviral FIX vector was intended for administration for humans and that greater efficiency of gene delivery was needed (page 119, column 1) and the teachings of Mason *et al.* and Takeuchi *et al.* that the complement-resistant retrovirus would be more efficient for *in vivo* gene delivery applications.

Applicants argue that the references do not provide a reasonable expectation of success in constructing complement-resistant retroviral particles capable of expression of FVIII which can be utilized in an *in vivo* clinical setting.

This argument has been fully considered but is not deemed to be persuasive. Applicants do not provide any reasoning or evidence to support the position that there is not a reasonable expectation of success. Furthermore, the claims are not drawn to retroviral particles which can be utilized in an *in vivo* clinical setting, just to retroviral particles, so an expectation of success *in vivo* is not required. The expectation that the vector could successfully be synthesized is extremely high. That is all that is necessary.

Conclusion

Claims 1-3, 6-11, 57, 58 and 61-68 remain rejected. Claims 37-56 are allowable. Claims 4 and 5 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 4-11, 37-56, 58 and 61-68 are free of the prior art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Schwartzman whose telephone number is (703) 308-7307. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703)-308-0196.

June 8, 2000

ROBERT A. SCHWARTZMAN
PATENT EXAMINER